Published in final edited form as:

Int Urogynecol J. 2019 November ; 30(11): 1817–1820. doi:10.1007/s00192-019-04011-x.

Small fiber polyneuropathy as a potential therapeutic target in interstitial cystitis/bladder pain syndrome

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Abstract

Introduction and Hypothesis: Interstitial cystitis/bladder pain syndrome (IC/BPS) and fibromyalgia (FM) are frequently co-occurring medical diagnoses in patients referred to the urology clinic for secondary and tertiary treatment options.

Methods: Abundant literature has shown that many patients with fibromyalgia have small fiber polyneuropathy (SFPN) that can be confirmed via skin punch biopsy and immunological staining to measure nerve density.

Results and Conclusions: This finding of SFPN provides a therapeutic target for fibromyalgia and in this article we hypothesize and provide rationale for the idea that this same phenomenon (SFPN) may explain, in some IC/BPS patients, the finding of widespread pain and likewise provide a therapeutic target for these patients.

Brief Summary

This hypothesis paper presents a rationale for evaluating small fiber polyneuropathy in interstitial cystitis/bladder pain syndrome patients as a potential therapeutic target for wide-spread pain.

Keywords

polyneuropathy; interstitial cystitis/bladder pain syndrome; fibromyalgia

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Conflict of Interest: The authors declare that they have no conflict of interest.

Introduction and Hypothesis

Polyneuropathy (peripheral neuropathy) describes a nontraumatic generalized disorder wherein multiple peripheral (i.e. outside of the brain and spinal cord) nerves become damaged, resulting in dysfunction and degeneration. Motor and sensory fibers are often affected equally, but polyneuropathy can affect *either* one, solely or very disproportionately. There are multiple types of peripheral neuropathy (most are *poly*neuropathies), classified according to the type of nerve damage, the underlying cause, and the associated symptoms. Symptoms include numbness and tingling, shooting pains in the limbs, fatigue, difficulty with motor coordination, and extreme sensitivity to touch. Polyneuropathy is known to be a feature of diseases such as alcoholism, autoimmune disorders (e.g. Guillain-Barre syndrome), chronic inflammatory demyelinating polyneuropathy and necrotizing vasculitis, as well as renal and liver diseases [1]. More recently, it has been well documented that polyneuropathy is a prominent feature of many pain-related illnesses and syndromes, including fibromyalgia [2].

Fibromyalgia, a neurologic and rheumatologic disorder characterized by chronic pain throughout the body and a heightened sensitivity to pressure, has no clearly defined etiology and is often a comorbid diagnosis in women suffering from other chronic pain disorders including interstitial cystitis/bladder pain syndrome (IC/BPS) [3–5]. IC/BPS patients experience pain and tenderness in their bladder and pelvic regions, have an increase in urinary urgency and frequency, and often experience discomfort or pain while engaging in sexual activity. Patients with urologic chronic pelvic pain syndrome (UCPPS), a blanket term that includes IC/BPS patients, often report pain outside the pelvic region which can be characterized as ‘widespread pain’ [6]. Our group (and others) has reported that women with a non-bladder centric form of IC/BPS frequently carry a multitude of comorbid pain diagnoses and experience chronic pain and discomfort throughout their bodies [5]. The etiology of this pain and hypersensitivity, particularly in BPS, could be linked to a systemic nerve disorder.

While the relationship between IC/BPS and polyneuropathy has not been unequivocally established, there are preliminary research findings that *small fiber* polyneuropathy (SFPN), a polyneuropathy subtype, exists in approximately 50% of patients with fibromyalgia (7). The confirmation of SFPN in these patients provided the first objective evidence that they were suffering from something beyond a “functional illness”. While SFPN manifests clinically in a variety of ways, diffuse pain is a characteristic complaint. SFPN is diagnosed by a *loss* of intra-epidermal nerve fiber density (IENF) on a skin punch biopsy [8], a finding that has been labeled as a “disruptive discovery” in fibromyalgia patients given its potentially groundbreaking impact [7]. While it may seem counterintuitive that a lower fiber density would be associated with *having* a pain syndrome, several recent studies have consistently shown a loss in IENF density in patients with neuropathic pain [9, 10]. In addition, SFPN may demonstrate structural abnormalities such as axonal swellings and sparse branching patterns [8]. Patients experiencing any sort of peripheral neuropathy experience changes and/or degeneration in the axotomy or gangliotomy.

Immunohistochemistry has been consistently used to visualize this phenomenon in individuals experiencing neuropathic pain [11].

SFPN has also been demonstrated in a small cohort of women with chronic pelvic pain. The majority of patients in this refractory chronic pelvic pain cohort had abnormal nerve conduction results and was diagnosed as positive for SFPN. Comorbid conditions noted in the study group included IC/BPS (18%), fibromyalgia FM (38%), endometriosis (15%), irritable bowel syndrome (33%), lower back pain (33%), migraine (38%), and other chronic pain syndromes (36%) [9]. Because the majority of CPP patients in this study experienced localized polyneuropathy, which is also recognized as commonly co-occurring in fibromyalgia [12], the diagnosis of fibromyalgia tends to be higher (as seen in this study) in these patients when compared to an IC/BPS diagnosis.

These findings, coupled with the substantial literature regarding SFPN and fibromyalgia pain, led us to hypothesize that because IC/BPS and fibromyalgia are often co-occurring conditions with substantial clinical overlap, and because fibromyalgia patients are often positive for SFPN, peripheral polyneuropathy may also underlie some of the *pain syndrome* aspects of IC/BPS. It is plausible that these comorbid pain syndromes that manifest throughout the body actually derive from a common pathogenic source. While no targeted treatments have yet been developed for SFPN, we believe that establishing SFPN as a pathogenic mechanism will be the first step towards more effective therapies. By taking a skin biopsy from our IC/BPS patients exhibiting fibromyalgia and polyneuropathy-like characteristics, we may be able to determine if an abnormal IENF density is a contributory element to their disease pathogenesis.

Methods and Results

Abnormalities in nerve density and function in patients with a suspected polyneuropathy can be evaluated through a relatively easy-to-procure skin punch biopsy. Using this approach, researchers were able to identify a difference in the intra-epidermal nerve fiber densities in 41 patients diagnosed with fibromyalgia versus 47 healthy controls [11]. In that study, all subjects underwent a routine 3-mm punch skin biopsy procedure from the proximal thigh and distal leg and the samples were analyzed to assess epidermal nerve fiber density (ENFD). Once collected, the biopsy samples were placed in 2% periodate-lysine-paraformaldehyde fixative and frozen. Following thick-sectioning, samples were immunohistochemically stained using an immune-peroxidase method for protein gene product 9.5, a ubiquitin carboxy-terminal hydrolase. Protein gene product 9.5 (PGP 9.5) is a cytoplasmic protein present in neural and neuroendocrine tissue that has been shown to be an excellent general marker of nerve fibers [13]. Visualization of nerve fibers within the skin tissue was performed using light microscopy and epidermal and dermal nerve fibers were quantified in the study subjects versus controls via a standard counting algorithm. Overall, women with fibromyalgia showed a significant decrease in ENFD from both the thigh (9.3 ± 3.2 in FM patients versus 11.3 ± 2.0 in the control subjects, $p=0.0007$) and calf (5.8 ± 2.8 in fibromyalgia patients versus 7.4 ± 1.9 in healthy controls, $p = 0.0002$). Furthermore, *age* and *calf ENFD* were inversely correlated in patients with fibromyalgia [11]. Figure 1 illustrates

the differences in ENFD density that are clearly visible via immunohistochemistry staining of skin biopsy tissue.

The same approach that has been used to assess nerve density and function in polyneuropathy has also been utilized for assessment of SFPN in patients who exhibit fibromyalgia-like symptoms. Using an identical method of skin punch biopsy procurement and processing, visualization of the intra-epidermal nerve fiber density in patients with diseases linked to SFPN could also be quantified by immunohistochemistry. In one such study that evaluated SFPN in 27 patients with fibromyalgia and 30 matched controls, where the visualization of sensory nerve endings in a distal-leg skin biopsy was accomplished using anti-PGP9.5 immuno-reactivity, the authors found that 41% of skin biopsies from subjects with FM, versus 3% of biopsies from control patients, were diagnostic for SFPN. In one representative finding from that study, a control subject was found to have a normal epidermal innervation density of 337 neurites/mm² of skin surface area (at the 76th percentile of the expected value) whereas a biopsy obtained from a fibromyalgia subject showed a markedly reduced IENF innervation of 135 neurites/mm² of skin surface area (at the 3rd percentile of the expected value) [2]. By using this approach to assess SFPN in skin punch biopsies from individuals with complex pelvic pain versus controls, we may be able to start to better understand the polyarthralgias and chronic widespread pain (CWP) that we often witness in our non-bladder centric IC/BPS population.

The emerging role of SFPN as a causative agent in pain syndromes has led researchers to hypothesize that a diagnostic skin biopsy would offer better insight to the concurrent pain syndromes present in individuals with chronic pelvic pain. In 2018, Chen et al reported the results of skin punch biopsies performed in a cohort of 39 women with refractory pelvic pain or multiple comorbid pain syndromes such as interstitial cystitis, fibromyalgia, lower back pain, endometriosis, and other complex regional pain syndromes [9]. Individuals with a diagnosis of a large fiber polyneuropathy such as multiple sclerosis, spine disease, or central nervous system trauma were excluded from the study. All subjects underwent 3 × 3 mm skin punch biopsies in the right upper thigh below the ischial tuberosity, the right lower thigh above the knee, and the right distal calf approximately 10 cm above the medial malleolus. These sites were chosen because of their quality of IENF densities. Once the samples were obtained, they were stained with PGP 9.5 and CD3 neuronal and immunological markers. The diagnosis of SFPN, in 25 of 39 patients (64%) was rendered by visually demonstrating a decrease in IENF density with immunofluorescence. This immunohistochemical staining technique simplifies the diagnosis of SFPN and permits expanded study in other pain populations.

Discussion

The results of skin punch biopsy testing and tissue processing with immunohistochemical techniques have opened a potential window of explanation into the varied and systemic pain manifestations in a subset of women previously labeled with the wastebasket terms of fibromyalgia, chronic pelvic pain, and chronic bladder pain syndrome [14]. The 3-mm skin punch biopsy could be used for evidence of a reduced IENF density in women with bladder pain syndrome, a finding that provides diagnostic confirmation of SFPN.

While approximately 50% of women with fibromyalgia have proven evidence of SFPN [12, 15], this polyneuropathy has not yet been the target of more focused treatment. Current management strategies largely revolve around drugs that affect general neuropathic pain such as tricyclic antidepressants (TCAs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) [8, 16]. These same drugs are also commonly used as Tier 2 empiric treatment options for IC/BPS according to the American Urology Association guidelines [17]. Other treatment strategies that have been tried in SFPN patients with fibromyalgia include intravenous lidocaine, IVIG, and other immunomodulatory therapies [8, 9] but none has been specifically used in IC/BPS patients. In addition to this, anti-muscarinic (medications which block the activity of the muscarinic acetylcholine receptors, inhibiting the conduction of action potentials in synapses in an effort to reduce pain) drugs, as well as psychosocial therapy and cognitive behavioral therapy have been used in patients with SFPN, BPS, and fibromyalgia [16].

Based on the available data, it is plausible that a subset of IC/BPS patients is affected by SFPN and could benefit from a targeted therapeutic approach, similar to what is anticipated for CPP and fibromyalgia patients with confirmed SFPN. This new avenue of research into an alternative explanation for women with non-bladder centric IC/BPS is rational and easily tested by a well-designed prospective trial. By following a protocol similar to what has been used in the studies cited here (i.e. taking a 3-mm skin punch biopsy from the distal leg to assess nerve density), it may be possible to facilitate a more complete understanding of the etiology behind the chronic widespread pain seen in our IC/BPS patient population. A decrease in IENF density would indicate that these individuals have SFPN, which could serve as an explanation and therapeutic target for their systemic disease manifestation.

In conclusion, although we are not aware of published evidence that confirms a role for SFPN in IC/BPS, the rationale for the hypothesis that SFPN *may* play an etiologic role in *some* IC/BPS patients comes primarily from the following observations: (1) a large percentage of patients with fibromyalgia, a common comorbid condition in IC/BPS, are also known to have confirmed SFPN and, (2) many IC/BPS patients appear to have a systemic pain disorder of uncertain etiology for which SFPN may present a logical explanation. We plan to apply the established skin biopsy techniques and immunohistochemical testing protocols for IENF density to a well characterized cohort of women with non-bladder centric IC to test this hypothesis.

Funding:

This study was funded by NIH/NIDDK Grant 5R21DK106554-02 (SJW).

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Figure 1.

(A) Skin biopsy specimen obtained from a normal subject, showing 4 nerve fibers (arrowheads) that extend from the dermis perpendicularly through the epidermis toward the upper layer of cells. (B) Skin biopsy specimen obtained from a patient with fibromyalgia and severe small fiber neuropathy, showing the total absence of epidermal nerve fibers and the presence of 1 nerve fiber in the dermis (arrowhead). The arrows indicate the dermal-epidermal junction. Protein gene product 9.5-stained and eosin-counterstained; bars 50 = μm . [reprinted with permission from reference 11].